REMARKS

Claims 1, 4, 8-11 and 19 are pending in this application. Claims 2, 3, 5-7, and 12-13 have been canceled without prejudice or disclaimer. Claims 14-18 have been withdrawn as being drawn to nonelected subject matter. Claims 1, 4, 9, and 19 have been amended. Claim1 has been amended to recite the limitations of claims 2, 6, 7, and 13. Claims 4 and 9 have been amended to more clearly define the limitations of the claim. Claim 19 was amended to correct the dependency of the claim. Support for the amendments to claims 1, 4, 9, and 19 can be found throughout the specification and claims as originally filed.

Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

No new matter has been added.

In view of the remarks set forth herein, further and favorable consideration is respectfully requested.

I. At pages 3-7 of the Official Action, claim 1 has been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

The Examiner acknowledges that the specification provides enablement for the use of either the free or fixed combination of ciclesonide with glycopyrronium and the enantiomers. However, the Examiner asserts that the specification is not enabling for the solvates or physiologically functional derivatives of the recited compounds.

Solely to expedite prosecution and not to be seen as acquiescing to the present

rejection, Claim 1 has been amended to only recite the combination of a pharmaceutical acceptable salt of glycopyrronium with ciclesonide and lactose monohydrate. The amended claims no longer include the limitations of the solvates or physiologically functional derivatives of the recited compounds, and therefore, render the rejection of claim 1 moot. Therefore, Applicants submit that the instant claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

II. At pages 7-14 of the Official Action, claims 2 and 3 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

The Examiner acknowledges that the specification provides enablement for free and fixed combinations. However, the Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the combination.

Claims 2 and 3 have been canceled without prejudice or disclaimer. Claim 1 has been amended to recite that the combination of a pharmaceutical acceptable salt of glycopyrronium, ciclesonide and lactose monohydrate is a fixed combination in the form of a dry powder. Therefore, the cancellation of claims 2 and 3 render this rejection moot for those claims. Applicants will address how this rejection does not apply to amended claim 1.

Applicants respectfully draw the Examiner's attention to page 4 of the present specification where the term "fixed combination" is defined as the simultaneous administration of combination of a pharmaceutical acceptable salt of glycopyrronium

with ciclesonide in the same pharmaceutical formulation. In contrast, the term "free combination" is defined as administered simultaneously or sequentially in different formulations.

The Examiner acknowledges these terms and their definitions in the specification on page 9 of the Official Action. However, the Examiner asserts that "[t]here is no further limitation of the definition of fixed and free to enable one to reproduce the invention." Applicants respectfully draw the Examiner's attention to pages 10 and 11 of the present specification. At page 10 of the specification, Examples 1-3 exemplify three powder inhaler embodiments and how those powder inhalers are made as ***fixed combinations***. Both the glycopyrronium and ciclesonide are combined in the same formulation as a powder which can be administered with a powder inhaler. Clearly from these examples, both the glycopyrronium and ciclesonide are contained within the same formulation meeting the definition of the term "fixed combination".

In contrast, Example 1 on page 11 exemplifies a ***free combination*** wherein the glycopyrronium and ciclesonide are formulated as seprate compositions. The glycopyrronium is provided as a DPI formulation while the ciclesonide is provided in a separate aerosol vial equipped with a dispensing valve. Clearly, the glycopyrronium and ciclesonide are contained in different formulations.

Applicants submit that not only are the terms "fixed combination" and "free combination" clearly defined on page 4 of the present specification, but the examples on pages 10 and 11 clearly enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the combination as a fixed or free combination without undue experimentation. Therefore, Applicants submit that the

instant claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

III. At pages 14-21 of the Official Action, claims 1-4, 10-13 and 19 have been rejected under 35 U.S.C. § 102(b) as anticipated by Keller et al. (U.S. Patent No. 6,645,466), as evidenced by the STN registry for glycopyrronium and ciclesonide

The Examiner asserts that claims 1-4, 10-13 and 19 are anticipated by Keller et al. as evidenced by the STN registry for glycopyrronium and ciclesonide since Keller et al. teach the use of magnesium stearate in dry powder formulations which contains a beta-mimetic and/or an anticholinergic and/or a corticosteroid or a pharmaceutically acceptable salt or ester in a dry powder formulation (fixed formulation) for inhalation along with lactose monohydrate.

Applicants note that claims 2, 3, 12 and 13 have been canceled without prejudice or disclaimer, and therefore the rejection as it applies to those claim is rendered moot.

Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

In the present application, independent claim 1, as amended, recites a pharmaceutical formulation consisting of a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, wherein the pharmaceutical acceptable salt of glycopyrronium is the enantiomerically enriched R,R-form, (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium, wherein the enantiomerically enriched R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee), and wherein the pharmaceutical formulation is a fixed combination in the form of a dry powder. Claims 4, 10, 11 and 19 depend, either directly or indirectly, on independent claim 1.

However, Keller et al. do ***not teach*** a pharmaceutical formulation ***consisting of*** a pharmaceutical acceptable salt of ***glycopyrronium in combination with ciclesonide, and lactose monohydrate***, wherein the pharmaceutical acceptable salt of glycopyrronium is the enantiomerically enriched R,R-form, (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium, wherein the enantiomerically enriched R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee), and wherein the pharmaceutical formulation is a fixed combination in the form of a dry powder. In contrast, Keller et al. teaches powder formulations in which magnesium stearate is required to improve the resistance to moisture. The presently pending claims do not recite the inclusion of magnesium stearate and recite the "consisting of" language to close the claim to the three components recited. Therefore, Keller et al. do not teach dry powder foumlations that do not include magnesium stearate.

Accordingly, Keller et al. fail to teach each and every elements of claim 1, as

required by Verda*gaal Bros. v. Union Oil Co. of California.*

As such, Keller et al. do not anticipate present claims 1, 4, 10, 11 and 19 within the meaning of 35 USC § 102(b). Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

IV. At pages 21-25 of the Official Action, claims 1 and 5-8 have been rejected under 35 U.S.C. §103 as being unpatenable over Keller et al. in view of Noe et al. (U.S. Patent No. 6,613,795).

The Examiner asserts that claims 1 and 5-8 are rejected under 35 USC § 103(a) as being obvious over Keller et al. in view of Noe et al.

As the basis for the rejection, the Examiner asserts that Keller et al. disclose powder formulations for inhalation which contain a pharmaceutically ineffective carrier of not-inhalable particle size and one or more finely divided pharmaceutically active compound of inhalable particle size and magnesium stearate. The Examiner acknowledges that Keller et al. do not disclose the recited ratio of enantiomerically enriched compound racemic forms of glycopyrronium for the preferred effectiveness.

Further, the Examiner asserts that the teachings of Noe et al. cure the deficiencies of Keller et al. The Examiner asserts that Noe et al. teach an enantiomerically pure glycopyrronium with at least 90% enantiomeric excess of the (3R, 2'R) configured enantiomer.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the enantiomers taught by Noe et al. instead of those taught by Keller et al. because of the advantages of i) dose reproducibility; ii) loses due to packing problems with the dry carriers; iii) degradation of the active groups and chiral rearrangement; and iv) shelf life taught by Noe et al.

According to the Examiner, the skilled artisan would have had a reasonable expectation of success in producing the present claims.

Applicants note that claim 6 and 7 have been canceled without prejudice or disclaimer, and therefore the rejection as it applies to those claim is rendered moot.

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007)*, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ... it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc.* v. *Chugai Pharm. Co.*, 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*. In addition, the cited references actually teach away from the limitations of the presently pending claims.

As stated above in section III, independent claim 1, as amended, recites a pharmaceutical formulation consisting of a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, wherein the pharmaceutical acceptable salt of glycopyrronium is the enantiomerically enriched R,R-form, (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium, wherein the enantiomerically enriched R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee), and wherein the pharmaceutical formulation is a fixed combination in the form of a dry powder. Claims 5 and 8 depend, either directly or indirectly, on independent claim 1.

Applicants note that the presently claimed subject matter is directed to a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate.

In contrast to the presently claimed subject matter, Keller et al. disclose powder formulations for inhalation which contain a pharmaceutically ineffective carrier of not-inhalable particle size and one or more finely divided pharmaceutically active compounds of inhalable particle size and magnesium stearate. Keller et al require the inclusion of magnesium stearate in the formulations to improve resistance to moisture. Nowhere in Keller et al. do they suggest powder formulations that do not include magnesium stearate. In fact, Keller et al. show in their examples that formulations that do not include magnesium stearate are less stable and produce formulations with less desirable fine particles doses or fine particle fractions (*See* the examples of Keller et al.). Keller et al. teaches away from dry powder compositions that do not include magnesium stearate. Therefore, Keller et al. fails to teach compositions consisting of a

pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate only.

Noe et al. do not remedy the deficiencies of Keller et al. Noe et al. teach an enantiomerically pure glycopyrronium with at least 90% enantiomeric excess of the (3R, 2'R) configured enantiomer that can be combined with a pharmaceutically acceptable carrier as a dry powder formulation.

However, like Keller et al., Noe et al. do not teach or suggest every element of the present subject matter. Nowhere do Noe et al. teach a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed.

Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*. In particular, none of the cited references teach or suggest a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed. In addition, the combination of references teaches away from dry powder formulations that do not contain magnesium stearate.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

V. At pages 25-28 of the Official Action, claims 1 and 9 have been rejected under 35 U.S.C. §103 as being unpatenable over Keller et al. in view of Paradissis et al. (U.S. Patent No. 5,133,974).

The Examiner asserts that claims 1 and 9 are rejected under 35 USC § 103(a) as

being obvious over Keller et al. in view of Paradissis et al.

As the basis for the rejection, the Examiner asserts that Keller et al. disclose powder formulations for inhalation which contain a pharmaceutically ineffective carrier of not-inhalable particle size and one or more finely divided pharmaceutically active compounds of inhalable particle size and magnesium stearate. The Examiner acknowledges that Keller et al. do not disclose twice or once daily treatment with the dry powder formulations for use in mammals or humans.

Further, the Examiner asserts that the teachings of Paradissis et al. cure the deficiencies of Keller et al. The Examiner asserts that Paradissis et al. teach twice or once daily use of pseudoephedrine in humans. Paradissis et al. does not disclose the use of glycopyrronium and ciclesonide in a nasal spray.

Applicants respectfully traverse this rejection. Again, to establish a prima facie case of obviousness, three requirements must be satisfied. First, a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The discussion of the presently claimed subject matter made in section IV above, particularly of claim 1, is incorporated herein by reference in its entirety. Accordingly,

the rejected claims 1 and 9 all require a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed.

The discussion of the Keller et al. reference, provided in Section IV above, is incorporated herein by reference in its entirety. Accordingly, Keller et al. fails to teach or suggest all the elements/limitations of claim 1 (and accordingly claim 9 also) because Keller et al does not teach a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed. In addition, Keller et al. requires the inclusion of magnesium stearate in their dry powder formulations.

Paradissis et al. do not remedy the deficiencies of Keller et al. Paradissis et al. teach twice or once daily use of pseudoephedrine in humans. Paradissis et al. does not disclose the use of glycopyrronium and ciclesonide in a nasal spray.

In addition, like Keller et al., Paradissis et al. do not teach or suggest every element of the present subject matter. Nowhere do Paradissis et al. teach a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed.

Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*. In particular, none of the cited references teach or suggest a dry powder formulation ***consisting of*** a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate, as presently claimed. In addition, the

combination of references teaches away from dry powder formulations that do not contain magnesium stearate.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 1, 4, 8-11 and 19. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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